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Review

Folic acid supplementation in pregnancy to prevent preterm birth: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Folic acid (FA) may have a role in the prevention of pregnancy complications. However, the efficacy of FA supplementation in reducing the risk of preterm birth (PTB) is still unclear. The aim of this systematic review with meta-analysis was to evaluate the efficacy of folic acid supplementation during pregnancy to prevent preterm birth (PTB). The research protocol was designed a priori, defining methods for searching the literature in electronic databases, including and examining articles, and extracting and analyzing data. We included all randomized trials (RCTs) of asymptomatic singleton gestations without prior PTB who were randomized to prophylactic treatment with either FA supplementation or control (placebo or no treatment). The primary outcome was the incidence of PTB <37 weeks. Five randomized trials including 5,332 asymptomatic singleton gestations without prior PTB were included in the analysis. Women who received FA supplementation had a similar rate of PTB <37 weeks (22.6% vs 22.9%; RR 0.99, 95% CI 0.82–1.18), PTB < 34 weeks (7.1% vs 8.7%; RR 0.77, 95% CI 0.55–1.09) and of preterm premature rupture of membranes (2.4% vs 2.9%; RR 0.81, 95% CI 0.44–1.50) compared with control group. Regarding neonatal outcome we found no significant differences in birth weight (mean difference 85.58 g, 95% CI -55.17–226.34), low birth weight (21.0% vs 15.1%; RR 0.79, 95% CI 0.49 to 1.28) and perinatal death (2.9% vs 2.4%; RR 0.90, 95% CI 0.60–1.34). In summary, FA supplementation during pregnancy does not prevent PTB <37 weeks. Daily FA supplementation remains the most important intervention to reduce the risk of neural tube defects.

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Introduction

Preterm birth (PTB) remains the number one cause of perinatal mortality in many countries, including the US [1]. Prior PTB is one of the most important risk factors for PTB; however, most of these PTBs occur in women without a prior PTB [2].

Folic acid (FA) is a water-soluble vitamin of the B group. Data from observational studies showed that FA, which is commonly used to prevent neural tube defects (NTDs) [3], may have a role in the prevention of pregnancy complications such as PTB, small for gestational age, preeclampsia and may lead to prolongation of pregnancy [4–7], However, the efficacy of FA supplementation in reducing the risk of PTB is still unclear [4–33].

The aim of this meta-analysis was to evaluate the efficacy of FA in decreasing the incidence of PTB in asymptomatic singleton gestations without prior PTB.

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1. Materials and methods

The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data. Searches were performed in MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, Scielo and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "micronutrients supplementation," "folic acid," "pregnancy," "folate" and "preterm birth" from inception of each database to October 2015. No restrictions for language or geographic location were applied.

We included all randomized trials (RCTs) of asymptomatic singleton gestations who were randomized to prophylactic treatment with either FA supplementation or control (either placebo or no treatment). Only trials on singleton gestations without prior PTB were included. Exclusion criteria included quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation); trials in women with multiple gestations; prior PTB; FA given also to controls; trials with only biochemical outcomes available; and trials evaluating other micronutrient supplementation in addition to FA.

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42014013874). The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [34].

Data abstraction was completed by two independent investigators (GS, VB). Each investigator independently abstracted data from each study and analyzed data separately. Differences were reviewed, and further resolved by common review of the entire data. All authors were contacted for missing data if possible.

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [35]. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias [35].Risk of bias was assessed by authors independently (GS, VB). Differences were resolved by consensus.

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was the incidence of PTB <37 weeks. Secondary outcomes were PTB <34 weeks, spontaneous PTB (sPTB) <37 weeks, sPTB <34 weeks, gestational age (GA) at delivery, latency, preterm premature rupture of membranes (PPROM) and neonatal outcomes including birth weight, low birth weight (LBW), admission to neonatal intensive care unit (NICU), neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), neonatal sepsis and perinatal death. We planned subgroup analysis including RCTs with FA supplementation of more than 1 mg daily.

The data analysis was completed independently by authors (GA, VB) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic. In case of statistically significant heterogeneity ($I^2 \geq 0\%$), the random effects model of DerSimonian and Laird was used to obtain the pooled relative risk (RR) estimate, otherwise in case of no inconsistency in the risk estimates ($I^2 = 0\%$) a fixed effect model was performed [35]. The summary measures were reported as RR with 95% confidence interval (95% CI). Potential publication biases were statistically assessed by using Begg's and Egger's tests [35]. p-value <0.05 was considered statistically significant.

Results

We initially identified 26 trials on FA supplementation during pregnancy [8–33]. No similar systematic reviews were found during the search process.

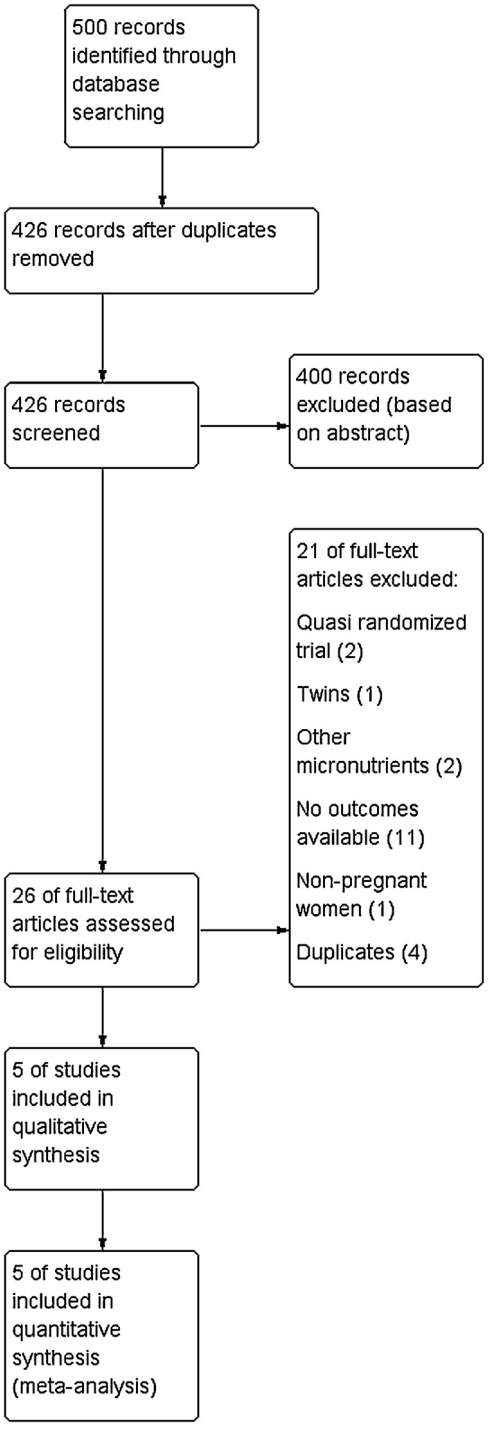

Fig. 1. Flow diagram of studies identified in the systematic review.

Twenty-one were excluded [13–33]. Two were excluded because they were quasi-randomized trial [13,14]; one because it evaluated the treatment also in twins [15]; two because they used also other micronutrients [18,19]; 11 because only biochemical outcomes were available [16,17,20–28]; one because it compared pregnant women with non-pregnant women [29], and four because they evaluated the same population of other included studies [30–33]. Five trials (5,332 women), which met inclusion criteria for this meta-analysis, were analyzed [8–12]. Fig. 1 shows the flow diagram (PRISMA template) of information through the different phases of the review.

The characteristics of the five included trials are summarized in Table 1. Three studies used iron both in treatment and in control groups. Three studies used FA 5 mg daily as treatment. Of the 5,332 asymptomatic singleton gestations without prior PTB in the five included trials, 1,912 (35.9%) were randomized to FA group, while 3,420 (64.1%) to control group. Publication bias, assessed statistically by using Begg's and Egger's tests, showed no significant bias ($p = 0.22$ and $p = 0.36$, respectively). The quality of RCTs included in our meta-analysis was assessed by Cochrane Collaboration's tool (Fig. 2). Three studies were double blind. None of the included studies had high risk of bias in "reporting bias" and "attrition bias".

The mean of GA at randomization was about 18 weeks in both groups. We found no differences in GA at delivery (mean difference 0.10 days, 95% CI -0.05–0.25) and in latency (mean difference -0.40, 95% CI -0.87–0.19) between the two groups. Women who received FA supplementation had a similar rate of PTB <37 weeks (22.6% vs 22.9%; RR 0.99, 95% CI 0.82–1.18; one study; Fig. 3), PTB <34 weeks (7.1% vs 8.7%; RR 0.77, 95% CI 0.55–1.09; one study) and of PPROM (2.4% vs 2.9%; RR 0.81, 95% CI 0.44–1.50; one study) compared with control group. Regarding neonatal outcome we found no significant differences in birth weight (mean difference 85.58 g, 95% CI -55.17–226.34; five studies), LBW (21.0% vs 15.1%; RR 0.79, 95% CI 0.49–1.28; four studies) and perinatal death (2.9% vs 2.4%; RR 0.90, 95% CI 0.60–1.34; two studies; Fig. 4) (Table 2). No data were available about sPTB <37 weeks, sPTB <34 weeks, NICU, RDS, BPD, IVH, NEC and neonatal sepsis. We also found no significant

Table 1
Descriptive data of included trials.

	Study location	Years	Number of patients at randomization	Intervention	Control	Blinding*	Primary outcome
Baumslag 1970[8]	South Africa	1968–1969	128 (65 vs 63)	FA 5 mg daily and 200 mg iron	200 mg iron only	Single blind	Rate of LBW
Fletcher 1971[9]	United Kingdom	1967–1969	643 (321 vs 322)	FA 5 mg daily and 200 mg iron	200 mg iron only	Double blind	Biochemical outcomes
Iyengar 1975[10]	India	N/A	230 (134 vs 96)	FA 0.5 mg daily and 60 mg iron	60 mg iron only	Double blind	Birth weight
Charles 2005[11]	United Kingdom	1966–1967	2365 (463 vs 1902)	FA 5 mg daily	Placebo	Double blind	Biochemical outcomes
Christian 2009[12]	Nepal	1998–2001	1966 (929 vs 1037)	FA 0.4 mg daily and Vitamin A (1000 g retinol equivalents)	Vitamin A (1000 g retinol equivalents)	Single blind	Preterm birth
Total	–		5332 (1912 vs 3420)	–	–		–

Data are presented as total number (*n* intervention vs control); FA: folic acid; mg: milligrams; LBW: low birth weight; N/A: not available. Doses of other micronutrients such as iron or vitamin A were identical in intervention and control groups.
*Single blind, blinding of outcome assessment; Double blind, blinding of outcome assessment as well as blinding of participants and personnel

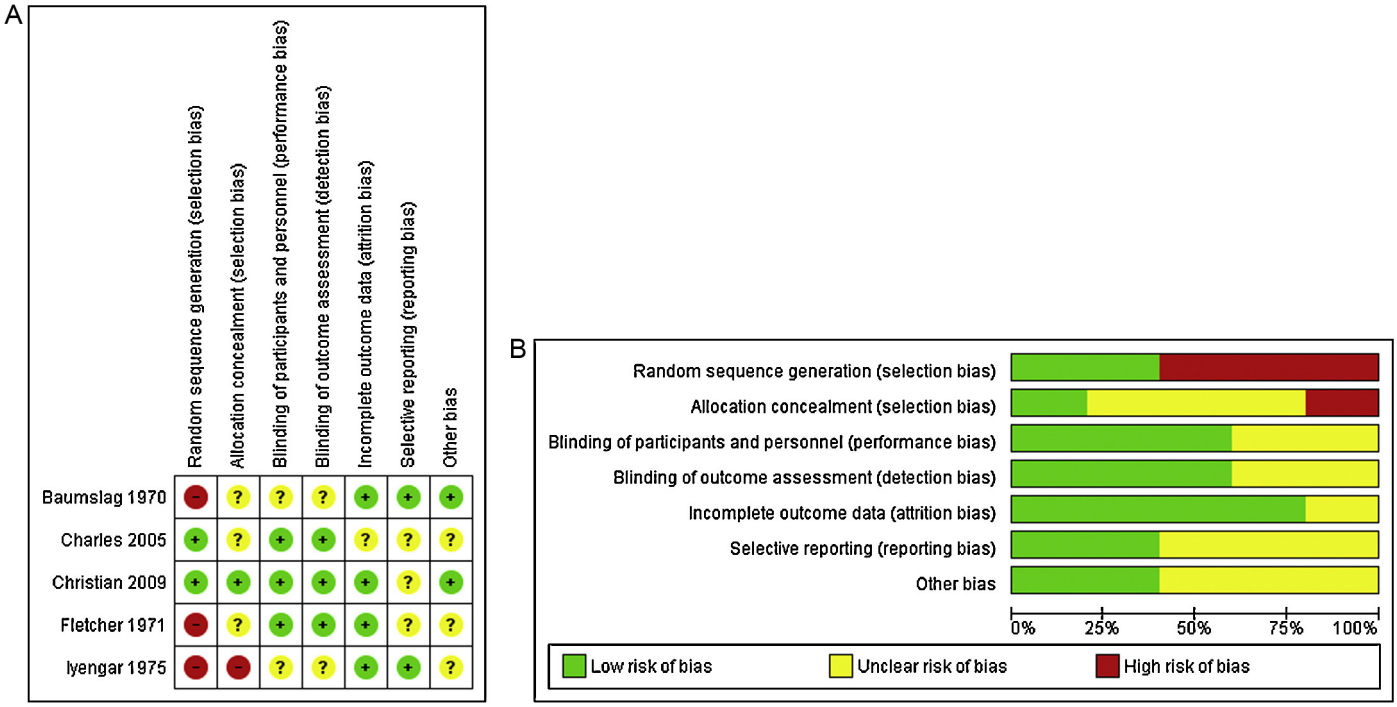

Fig. 2. Assessment of risk of bias. (a) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (b) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

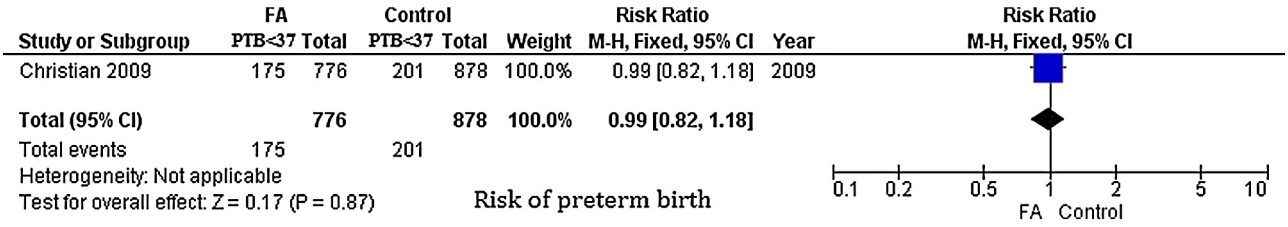

Fig. 3. Forest plot for the risk of preterm birth less than 37 weeks. FA, folic acid; PTB, preterm birth; CI, confidence interval; M-H, Mantel-Haenszel test.

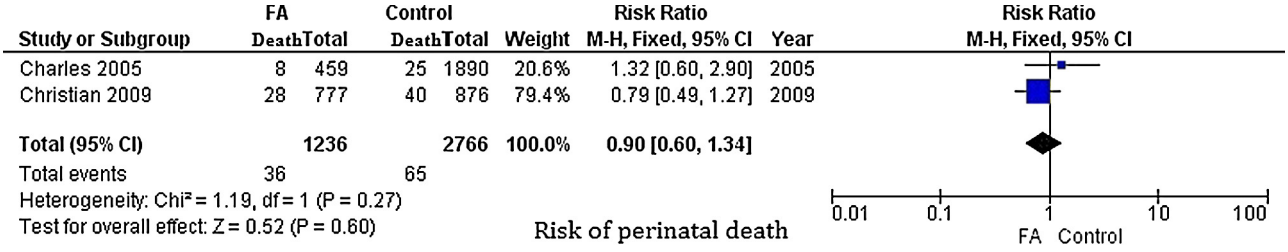

Fig. 4. Forest plot for the risk of perinatal death. FA, folic acid; Death, perinatal death; CI, confidence interval; M-H, Mantel-Haenszel test.

differences in the primary and secondary outcomes assessed in the subgroup analysis (Table 3).

Comment

This meta-analysis of the five RCTs evaluating the efficacy of FA supplementation in preventing PTB in 5,332 asymptomatic singleton gestations without prior PTB shows that FA supplementation is not associated with prevention of PTB or improved neonatal outcomes.

Prior evidence from observational studies showed that, compared with standard low-dose supplementation, additional folic acid may prolong gestation, especially if started preconception [4–7]. Biologically, the authors point to anti-inflammatory mechanism [4,7]. There are several hypotheses that could link FA and prevention of PTB. First, periconception FA supplementation may influence early placentation processes and placental development regulating the secretion of matrix metalloproteinases [36]. Second, micronutrient status at the time of implantation and homocysteine levels could have a role in inflammation [37]; in fact early PTB is often caused by intrauterine infection and inflammation [38]. Furthermore, an experimental study on mice showed that FA supplementation during pregnancy prevents PTB, fetal death and intrauterine growth restriction by an anti-inflammatory mechanism [39].

Given that FA is recommended for all women during pregnancy [3], focusing on whether the use of higher dose of FA leads to further improved outcomes such as PTB prevention would be helpful. However, we found no RCTs evaluating the efficacy of high-dose compared with low-dose FA; two RCTs are currently ongoing [40,41]. However, even in our subgroup analysis, high-dose FA

Table 2
Primary and secondary outcomes.

	GA at randomization mean (weeks)	GA at delivery mean (weeks)	Latency mean (days)	PTB < 37 weeks	PTB < 34 weeks	PPROM	Birth Weight, mean (grams)	LBW	Perinatal death
Baumslag 1970[8]	26 vs 26	N/A	N/A	N/A	N/A	N/A	1547 vs 1520	4/65 (6.2%) vs 19/63 (30.2%)	N/A
Fletcher 1971[9]	N/A	N/A	N/A	N/A	N/A	N/A	3330 vs 3330	24/321 (7.5%) vs 16/322 (5.0%)	N/A
Iyengar 1975[10]	N/A	N/A	N/A	N/A	N/A	N/A	2890 vs 2650	N/A	N/A
Charles 2005[11]	18 vs 18	40 vs 40	158 vs 158	N/A	N/A	N/A	3319 vs 3299	20/459 (4.4%) vs 115/1890 (6.1%)	8/459 (1.7%) vs 25/1890 (1.3%)
Christian 2009[12]	11 vs 11	38 vs 38	190 vs 191	175/776 (22.6%) vs 201/878 (22.9%)	52/776 (7.1%) vs 76/878 (8.7%)	17/715 (2.4%) vs 24/822 (2.9%)	2587 vs 2587	262/628 (41.7%) vs 297/685 (43.4%)	28/777 (3.6%) vs 40/876 (4.6%)
Total	18 vs 18	39 vs 39	160 vs 161	175/776 (22.6%) vs 201/878 (22.9%)	52/776 (7.1%) vs 76/878 (8.7%)	17/715 (2.4%) vs 24/822 (2.9%)	2842 vs 2796	310/1473 (21.0%) vs 447/2960 (15.1%)	36/1236 (2.9%) vs 65/2766 (2.4%)
Mean difference (95% CI) or RR (95% CI)	0.11 weeks (95% CI -0.12 to 0.30)	0.10 days (95% CI -0.05–0.25)	-0.40 days (95% CI -0.87–0.19)	0.99 (95% CI 0.82–1.18)	0.75 (95% CI 0.53–1.04)	0.81 (95% CI 0.44 to 1.50)	85.58 grams (95% CI -55.17–226.34)	0.79 (95% CI 0.49–1.28)	0.92 (95% CI 0.58–1.46)

Data are presented as number intervention vs number control or as total number (*n* intervention vs control); GA: gestational age; PTB: preterm birth; LBW: low birth weight; PPROM: preterm premature rupture of membranes; N/A: not available; RR: risk ratio; CI: confidence interval; RCTs: randomized controlled trials; FA: folic acid. Neonatal and delivery outcomes were referred to live-born only

Table 3
Primary and secondary outcomes in subgroup analysis including trials with folic acid supplementation of ≥ 1 mg daily.

	GA at randomization mean (weeks)	GA at delivery mean (weeks)	Latency mean (days)	PTB < 37 weeks	Birth Weight, mean (grams)	LBW	Perinatal death
Baumslag 1970[8]	26 vs 26	N/A	N/A	N/A	1547 vs 1520	4/65 vs 19/63	N/A
Fletcher 1971[9]	N/A	N/A	N/A	N/A	3330 vs 3330	24/321 vs 16/322	N/A
Charles 2005[11]	18 vs 18	40 vs 40	158 vs 158	N/A	3319 vs 3299	20/459 vs 115/1890	8/459 vs 25/1890
Total	21 vs 21	40 vs 40	158 vs 158	N/A	2433 vs 2409	48/845 (5.7%) vs 150/2275 (6.6%)	8/459 (1.7%) vs 25/1890 (1.3%)
RR (95% CI)	Mean difference 0.50 week (95% CI -0.52–0.30)	Mean difference 0.10 days (95% CI -0.05–0.25)	Mean difference -0.70 days (-0.80–0.60)	N/A	Mean difference 81.29 grams (95% CI -57.24–219.83)	0.66 (95% CI 0.27–1.63)	1.32 (95% CI 0.60–2.90)

Data are presented as number intervention vs number control or as total number (*n* intervention vs control); GA: gestational age; PTB: preterm birth; LBW: low birth weight; PPROM: premature rupture of membranes; N/A: not available; RR: relative Risk; CI: confidence interval; RCTs: randomized-controlled trials; FA: folic acid. Neonatal outcomes were referred to alive-born only

supplementation was not associated with prevention of PTB compared with control, but data were limited.

Another meta-analysis has evaluated the efficacy of FA in prevention of PTB. However, this meta-analysis did not exclude RCTs with FA as control, RCTs with multiple gestations, RCTs on women with prior PTB, and RCTs evaluating also other micronutrients. This review found no conclusive benefit of FA supplementation during pregnancy on pregnancy outcomes [42].

One of the strengths of our study is inclusion of RCT data on FA supplementation during pregnancy in a specific population, i.e. asymptomatic singleton gestations without prior PTB. This population represents, in all countries, usually about 90% or more of the pregnant population. We chose to limit inclusion of studies to this population as other interventions to prevent PTB have been shown to have different results in different populations of pregnant women. For example, progesterone supplementation, as well as cerclage, has differing effects in populations such as singleton without prior PTB versus singletons with prior PTB versus multiple gestations [43–52]. Another strength of our study is that we planned a subgroup analysis to evaluate just high-dose FA supplementation. One author provided additional and unpublished data from the original trial [12].

Limitations of our study are inherent to the limitations of the included RCTs. Most of the included studies were conducted during the 1970s, so that we found poor compliance with random allocation. None of the studies randomized FA preconceptionally. Only one RCT had PTB as primary outcome. The dosage of FA differed somewhat among studies. While no included study mentioned that women enrolled had a prior PTB, this characteristic was not always reported. The study by Christian et al. is the only one that contributed to the primary outcome, and it was conducted in Nepal which is a unique low-resource setting. This limitation raises the question of external generalizability to the current US population. Preterm delivery rates were very high (about 23%) for asymptomatic singleton gestations without prior PTB, but were based on the Christian study alone.

There may be other explanations for the fact that our data show no association between FA supplementation and prevention of PTB. First, FA supplementation may have been given too late. The mean GA at randomization was about 18 weeks, and most other interventions to prevent PTB, such as progesterone, cerclage or omega-3, have usually shown efficacy when implemented earlier [43,44,50,51]. Second, it could be that FA supplementation is only beneficial in women with FA deficiency, a variable which was not evaluated in the included RCTs. Finally, it could also be that FA supplementation is truly not effective in preventing PTB.

In summary, FA supplementation cannot be currently recommended solely for prevention of PTB. Given the limitations of this meta-analysis, further large, well-designed, placebo-controlled trials are needed. Daily FA supplementation remains the most important intervention to reduce the risk of NTDs.

Conflicts of interest

The authors report no conflict of interest

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